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Spleno-hepatoplasty in Rats with Chemically-induced Cirrhosis of the Liver

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Abstract

It is well known that cirrhosis of the liver shows a characteristic pathohistological alteration of the lobular architecture and is accompanied with complications such as portal hypertension, ascites, esophageal varices and malignant transformation of the liver parenchymal cells. Many investigators and surgeons have devised various surgical methods for the treatment of some of these complications. BENICHOUX and BARLIER[1] reported in 1964 that spleno-hepatoplasty (SHP) was an effective procedure. However, they did not describe the basic mechanism of SHP. The present study was, therefore, designed to investigate it in rats in which cirrhotic changes in the liver were produced by the administration of carbon tetrachloride or thioacetamide.

The partially-decapsulated spleen with vascular pedicles was implanted into the left lobe. Liver function, weight and portal venous pressure were determined and analyzed statistically. Angiographic and histological studies were performed in all of the animals receiving SHP. Portal venous pressure, serum glutamic pyruvic transaminase and alkaline phosphatase tended to return to normal in the two-SHP groups. However, neither histological improvement of the cirrhotic changes nor hypertrophy of the lobe into which the spleen was implanted was demonstrated, while angiography revealed patency of the vascular communications between the liver and the spleen in the majority of the animals receiving SHP. It was concluded that not only augmentation of the blood supply from the spleen to the liver but also the development of pathways between the hepatic venous and portal venous branches seemed to be responsible for the decompression of portal hypertension, although SHP is a paradoxical procedure for the treatment of cirrhosis of the liver.

Key words : Spleno-hepatoplasty (SHP), Portal venous pressure (PVP), Serum glutamic pyruvic transaminase (SGPT), Alkaline phosphatase, Carbon tetrachloride (CCl_4), Thioacetamide (TA), Partial hepatic lobectomy (PHL) and Splenectomy (STY).
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Introduction

Cirrhosis of the liver is characterized pathohistologically by typical changes in the normal lobular arrangement caused by degenerative and regenerative processes in the liver parenchyma. It has been a major clinical problem to control complications such as portal hypertension, esophageal varices, etc. It is desirable to restore the distorted architecture to normal by enhancing regeneration of the liver cells and inhibiting hyperplasia of the fibrous connective tissue. Unfortunately, however, there is no way to do this. The present study was designed to determine whether or not SHP is an effective treatment of cirrhosis, and if so, what mechanism plays the major role in this respect.

Experimental cirrhosis of the liver was produced in male albino rats by the administra ion of carbon tetrachloride or thioacetamide. SHP was performed in rats in which cirrhosis was confirmed by gross examination at laparotomy. Liver chemistry studies, measurement of portal venous pressure and histological examinations were performed in all the animals used in the study.

Materials and Methods

Animals

Two hundred and thirty-one male albino rats of the Wistar strain weighing approximately 200g were placed in screen-floored cages and maintained on a pellet diet and water ad libitum. They were divided into two cirrhosis-induced groups and a control group; the former were further divided into subgroups which will be described later.

Diet

The ingredients of the stock pellet diet, a product of Nihon Clea, Tokyo, are listed in Table 1. The average intake of diet and water was 25g/day and 28ml/day at 26°C, respectively.

Table 1. Ingredients of the pellet diet, CE-2, Nihon Clea.

Water	6.0(g)	Vitamin E	2.3 (mg)
Protein	24.0	Vitamin B_1	1.3
Fat	3.5	Vitamin B_2	1.3
Carbohydrate	56.0	Vitamin B_6	1.1
Fibre	4.5	Vitamin B_{12}	3.0 (mcg)
Ash	6.0	Pantothenic acid	1.9 (mg)
Calories	351.5(Cal)	Nicotinic acid	11.6
Vitamin A*	1000 (IU)	Folic acid	0.1
Vitamin D*	200 (IU)	Choline	228
(* supplemented)			
Ca	1.0 (g)	Mn	6.00(mg)
P	1.0	Fe	10.00
Mg	0.27	Ca/P	1.00
Na	0.31	Ca/Mg	3.70
K	0.85	K/Na	2.74

Production of Cirrhosis

a) Cirrhosis induced by CCl_4 : The rats were transferred to a wooden chamber with a peep-window, and a capacity of 256.5 *l*. CCl_4 was vaporized in a series of colored bottles through which compressed oxygen was passed at a constant flow rate of 3.0 *l*/min, CCl_4-gas was introduced into the chamber through an inlet tap near the floor, leaking through the slit between the chamber and the cover when the chamber was filled with the gas. In every poisoning, the gas was kept flowing for a given period of time and the animals were confined in the chamber for an equal period of time after the cessation of vaporizing CCl_4. This group was given water containing sodium phenobarbital in a concentration of 0.5g/*l* starting one week before exposure to CCl_4 and continuing through the experiment. The first poisoning lasted six minutes and thereafter ten. The frequency was twice a week. The average body weight was 199g at the start of CCl_4-gassing, it reached 380g after ten weeks. In the early stages of gassing the majority of rats suffered from cough and/or hyperemia of the conjunctivae, and later on some of them died of hematemesis, melena and/or emaciation. Twenty-six of the rats died, a mortality rate of 19 per cent.

b) Cirrhosis induced by TA: Four per cent aseptic aqueous solution of thioacetamide was prepared. It was administered intraperitoneally in a dose of 20mg/100g of body weight, three times a week for eight to ten weeks. Sodium phenobarbital was not given to the animals of this group. The average intial body weight was 215g ; it increased to 296g in eight weeks. Nine rats died of intraperitoneal bleeding and/or emaciation (18 per cent).

Spleno-hepatoplasty

The rats were anesthetized by intraperitoneal injection of Nembutal, 5mg/100g of body weight. The abdomen was entered via a mid-line incision. The spleen was first freed from its surrounding ligaments and adhesions by sharp dissection and/or ligation and was brought out of the wound without injuring the splenic blood vessels. The left lobe of the liver was pulled upward through the wound. A small partial resection was made in the form of a triangle or trapezoid at the edge of the lobe, and the spleen was trimmed to fit the defect of the lobe. The splenic portion was wedged into the left lobe and fixed with non-traumatic 6-0 Nylon, as shown in Figure 1. The wound was closed in layers and the animal returned to its cage after complete recovery from anesthesia. It took about 12 minutes to complete this oparation, and about 30 minutes to measure the portal venous pressure and/or to collect blood for analysis from the portal vein. The weight of the resected lobe for SHP ranged from 0.24g to 0.47g. The operative mortality was 30 per cent in the CCl_4-group, 20 per cent in the TA-group and 21 per cent in the control group. A representative example of SHP is shown in Figure 2.

Partial Hepatic Lobectomy (PHL)

Under Nembutal anesthesia, the abdomen was opened via a mid-line incision. The left lobe was resected to the same extent and shape as the SHP. The defect left behind the PHL was closed by anchoring with interrupted non-traumatic Nylon, followed by closure of the main wound.

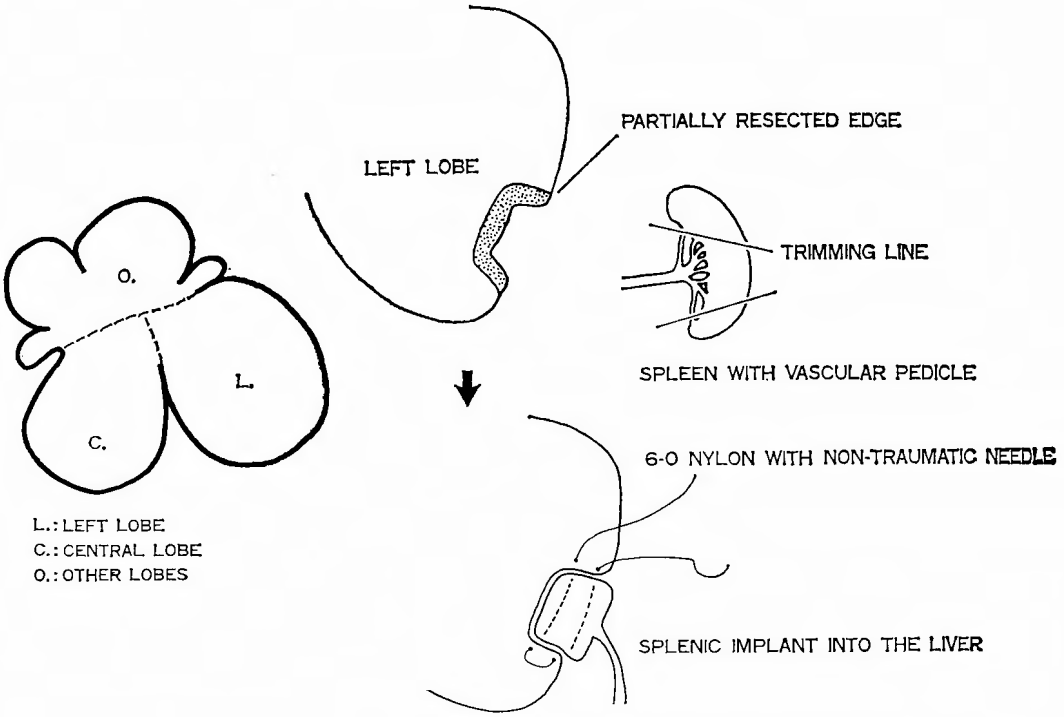

Figure 1

Figure 1. Left : Schematic illustration of rat liver divided into three parts by dotted lines into left, central and other lobes. Figures on the right illustrate procedure of spleno-hepatoplasty.

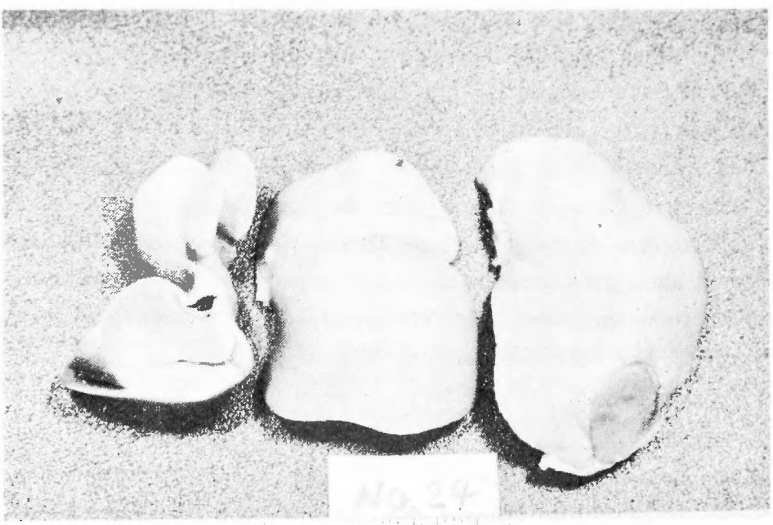

Figure 2. An example of spleno-hepatoplasty. Other lobes (left), central lobe (middle) and left lobe with wedged spleen (right).

Splenectomy (STY)

Under anesthesia the abdomen was entered via a mid-line incision. The spleen was removed by sharp dissection and ligation. The mean ratio of the splenic weight to body weight was 0.56 per cent in the CCl_4-group and 0.42 per cent in the TA-group. The difference in the mean ratio between the two groups may be due to phenobarbital which is said to cause congestion of the liver and spleen[2].

Angiography

a) *Arterial Angiography* : Angiography was performed to confirm the development of vascular communications between the spleen and the liver in the rats which survived several weeks or months after SHP. Under routine anesthesia, rats were killed by blood-letting from the abdominal aorta. The chest was then opened and a 23-gauge elastic catheter was inserted into the thoracic aorta. The hepatic artery, the portal trunk and the other blood vessels to the liver, e.g. the left gastric and esophageal arteries[3] were all transected by ligation, and finally the liver was freed from the diaphragm and the hepatic vein, so that the splenic vascular bundle was the only hepatopetal pathway. The left lobe was perfused with warm heparinized saline via the indwelling catheter in the thoracic aorta prior to the injection of radiopaque or chemical dye.

b) *Venous Angiography* : Under routine anesthesia, the abdomen was reopened and a 23-gauge needle with wings was inserted into the mesenteric vein and tied with fine silk thread, while the portal trunk was divided by double ligation and the liver was dissected free from the diaphragm and the hepatic vein. Through this needle radiopaque or chemical dye was injected. In many instances the left lobe was stained diffusely more than in arterial angiography when India ink was injected via the needle, as shown in Figure 3.

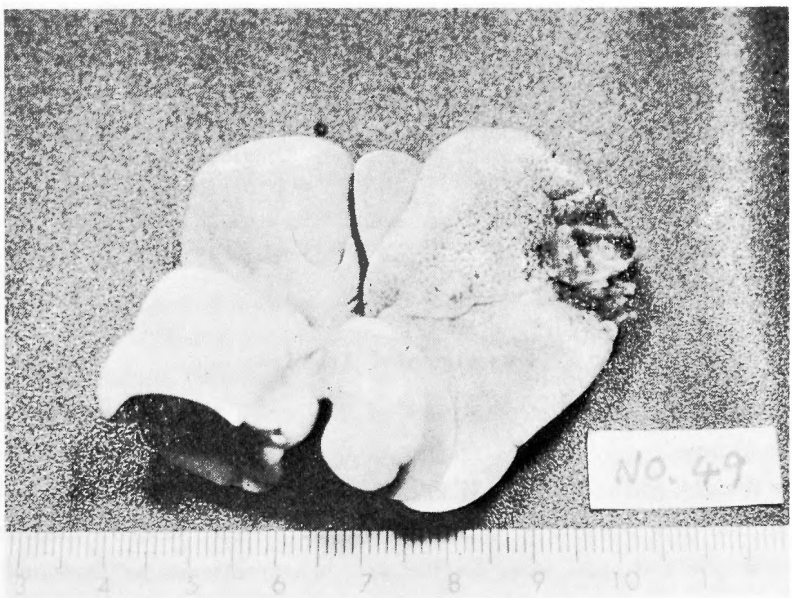

Figure 3. The left lobe is stained diffusely by India ink injected via the splenic vein.

Experimental Groups

The rats with cirrhosis induced by CCl_4 were subdivided as follows : (a) CCl_4-inhalation, (b) CCl_4-inhalation with SHP, (c) CCl_4-inhalation with PHL, (d) CCl_4-inhalation with splenectomy and (e) long-survival after CCl_4-inhalation. The rats in which cirrhosis was induced by TA were divided into the following subgroups : (a') TA-injection, (b') TA-injection with SHP, (d') TA-injection with splenectomy and (e') long-survival after TA-injection. The group with TA-injection and PHL was omitted from the study, because all of the animals died. In addition to these groups, group (f) was used to observe effect of phenobarbital on the liver. The rats in this group received phenobarbital only. The controls were in group (g). Another group (h) consisted of normal rats in which only SHP was performed in an investigation of the effect of SHP on the development of vascular communications between the liver and the spleen. It is said that chemically-induced cirrhosis of the liver in rats tends to recover rapidly when administration of the cirrhogenic substance is discontinued[1] Therefore, the rats in groups (b), (c), (d), (b') and (d') were treated with further CCl_4-inhalation or TA-injection for five to eight weeks after a postoperative intermission of one week. Group (a) and (a') were treated in the same way.

Table 2. Rats in which cirrhosis was induced by inhalation of carbon tetrachloride (CCl_4) were divided into five subgroups: (a), (b), (c), (d) and (e). Those with cirrhosis of the liver induced by thioacetamide (TA) were subdivided into four groups: (a'), (b'), (d') and (e'). Group (f) was used to investigate the effect of phenobarbital on the liver and group (h) received spleno-hepatoplasty only. Group (g) was the control group.

Groups of Male Albino Rats

Cirrhosis induced by CCl_4	Cirrhosis induced by TA
(a) CCl_4-Inhalation	(a') TA-Injection
(b) CCl_4-Inhalation c Spleno-Hepatoplasty	(b') TA-Injection c Spleno-Hepatoplasty
(c) CCl_4-Inhalation c Partial Hepatic Lobectomy	(--) ———
(d) CCl_4-Inhalation c Splenectomy	(d') TA-Injection c Splenectomy
(e) Long-Survival After CCl_4-Inhalation	(e') Long Survival After TA-Injection
(f) Phenobarbital s CCl_4-Inhalation	
(g) Control	(g) Control
(h) Spleno-Hepatoplasty Only	

Experimental Articles

Six to eight days after the completion of CCl_4-or TA-administration, the following studies were performed.

a) Liver Weight, Ratio of Liver Weight to Body Weight and Weights of the Resected Lobes : In rats the liver consists of five lobes. In the present study it was trisected into left lobe, central lobe and other lobes for the sake of convenience, as illustrated in Figure 1. Body weight was measured before the animals were sacrificed, and the liver was removed and trisected after sacrifice. The wet weight of each liver lobe was measured, followed by

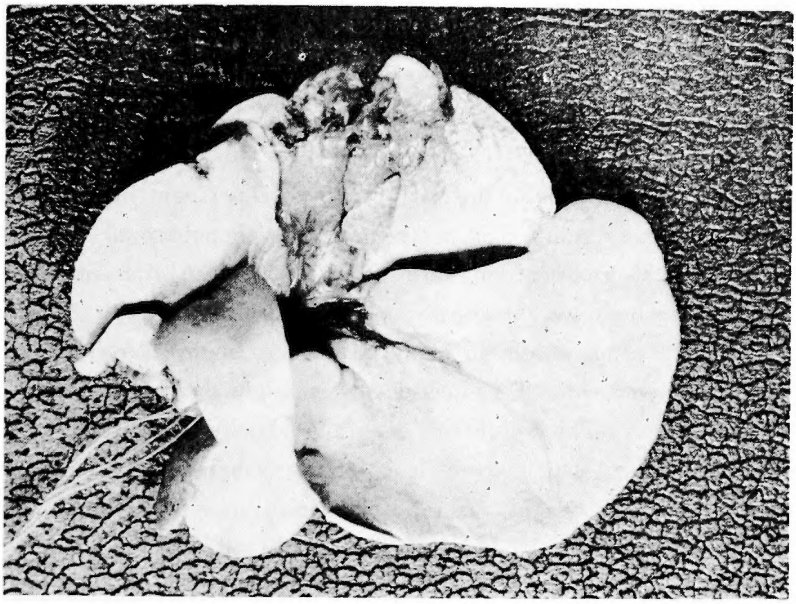

Figure 4. The middle portion of the lobe is stained by India ink injected via the splenic artery.

calculation of total liver weight and liver to body weight ratio. In the SHP-groups, the weight of the splenic portion attached to the left lobe was included.

b) *Liver Chemistry Studies* : Blood was drawn from the heart ventricle by puncture or via the needle placed in the mesenteric vein after measurement of the portal venous pressure. Serum was separated from blood by centrifugation. Serum glutamic pyruvic transaminase was determined by Reitman-Frankel's method and experessed in Karmen units. Alkaline phosphatase was measured by K-K simplified method and expressed in King-Armstrong units. Electrophoretic analysis of the serum was tried but it failed because of contamination with fibrin or fibrinogen. Total serum protein was determined.

c) *Measurement of Portal Venous Pressure(PVP)* : The value of PVP was read on a scale attached to a glass tube filled with heparinized saline warmed to 38°C. The zero lovel for measuring PVP was set at the level of the ventral surface of the spinal vertebra with the rat lying on its back. A semi-conducting transducer made by Hitachi Koden was used for the determination of PVP but no difference was found between the two methods, proving that the present method was reliable[5].

d) *Histological Examination* : After being weighed, the extirpated liver was fixed in 10 per cent formalin solution for one week. A test piece was taken from each section of the trisected liver, embedded in paraffin and sliced in 6μ pieces. The sections were stained with hematoxylin and eosin or Van Gieson's picrofuchsin.

e) *Angiographic Examin ıtion* : In the majority of animals with SHP, arterial or venous angiography was performed.

Results

a) Liver Weight, Liver to Body Weight, Ratio and Weight of Each Section of Trisected Liver : The results are summarized in Table 3. In the CCl_4-group, except for the long-term survivors after CCl_4-inhalation, liver weight and the liver to body weight ratio showed a significant increase; 4.26 per cent in the SHP-group, 4.58 per cent in the PHL-group, 5.47 per cent in the splenectomy-group, 5.59 per cent in the phenobarbital group and 3.36 per cent in the control. In the group of long-term survivors after CCl_4-inhalation the liver weight and the ratio of liver to body weight approximated those of the control. The trisected liver sections were nearly the same weight in many instances. In the TA-group, except for the group of long-term survivors after TA-injection, liver weight and the ratio of liver to body weight returned to normal. The weights of each lobe showed no marked difference as in the CCl_4-group. In the rats which lived long after receiving SHP only, no signficant difference was found in liver weight, the ratio of liver to body weight or weight of each lobe, as compared with the controls. It is in general believed that the ratio of liver to body weight is higher in young rats than in old[6]. It was three to four per cent in the rats weighing more than 300g in the present study. It is well known that sodium phenobarbital increases the susceptibility of the liver to carbon tetrachloride and the contents of fat and water in the liver parenchymal tissue[7]. It is also well known that TA causes nuclear swelling of the liver cells and increase water concentration in the liver[8]. In the two cirrhotic

Table 3. Mean values and standard deviations of body weight and liver weight, mean ratios of liver weight to body weight and mean weight of resected lobes in all the experimental groups used in the present study. SHP-Spleno-hepatoplasty, PHL-Partial hepatic lobectomy, STY-Splenectomy, L-Left lobe, C-Central lobe and O-Other lobes.

	n	Body WT.	Liver WT.	L.W. B.W.	L.g	%	C.g	%	O.g	%
(a) CCl_4-Inhalation	8	460±48	22.59±4.00	4.89	8.58	38	6.49	29	7.52	33
(b) CCl_4-INH c SHP	7	426±59	17.99±3.20	4.26	7.25	40	5.18	29	5.56	31
(c) CCl_4-INH c PHL	5	425±36	19.48±6.04	4.58	8.19	42	4.78	25	6.51	33
(d) CCl_4-INH c STY	5	465±56	25.48±3.47	5.47	9.37	37	7.12	28	9.00	35
(e) Long-Survival After CCl_4-INH	16	414±71	14.95±2.84	3.61	5.34	36	4.70	31	4.91	33
(f) Phenobarbital c CCl_4-Inhalation	5	516±31	28.88±4.03	5.59	9.43	33	10.45	36	8.99	31
(g) Control	25	419±70	14.09±2.38	3.36	4.75	34	4.87	34	4.42	32
(h) Long-Survival After SHP	12	475±77	14.77±3.73	3.11	4.83	33	5.00	34	4.94	33
(a') TA-Injectied	8	333±49	18.13±5.56	5.44	6.68	37	6.22	34	5.23	29
(b') TA-Inj c SHP	6	342±51	20.79±6.34	6.08	6.88	33	7.47	36	6.44	31
(d') TA-Inj c STY	6	334±32	21.17±1.80	6.34	8.07	38	6.41	30	6.69	32
(e') Long-Survival After TA-Inj	5	422±48	14.63±3.47	3.44	5.42	37	4.69	32	4.52	31

groups, the liver weight gradually decreased after the cessation of administration of the cirrhogenic agents. This may be due to the vigorous healing tendency of experimentally-induced cirrhosis of the liver in rats as well as the reversible effect of these cirrhogenic agents. No weight gain was found in the left lobe of either SHP group, suggesting that the nourishing effect of SHP on this lobe was minimal, although blood inflow was ascertained. Two normal rats receiving SHP were reoperated 70 days after to see if they could survive sudden complete obstruction of the portal venous trunk; they died about ten hours after the obstruction. This suggests that the amount of blood which was delivered to the liver through SHP was too small to equal the pre-existing hepatic inflow of the portal venous blood.

b) Liver Chemisity Studies : The results are listed in Table 4. The splenectomy group (d) showed the highest mean value of SGPT, while that of group (b) was significantly lower than that of the other groups, as shown in Figure 5. Among the TA-groups, the splenectomy group (d') showed the highest value of SGPT while the SHP-group (b') showed a significantly lower mean value than the other group, (a') and (d'), in much the same way as the CCl_4-groups, as shown in Figure 8. Alkaline phosphatase in the CCl_4-groups was higher than in the control groups, but it was lower than in the other groups, (a), (c) and (d). The difference in alkaline phosphatase between (a) and (b) as well as (b) and (c) was significant statistically, as shown in Figure 6. In the TA-groups, the SHP-group showed a higher value than the control group but the difference among the three groups, (a'), (b')

Table 4. Mean values and standard deviation of SGPT, alkaline phosphatase (Alk-p-ase), total serum protein (TSP) and portal venous pressure (PVP) in all experimental group. SGPT is expressed in Karmen units, Alk-p-ase in king-Armstrong units, TSP in g/dl and PVP in cmH_2O. plasma from the mesenteric vein instead of serum was used for the determination of TSP.

	n	s GPT	ALK-P-ASE	TSP	PVP
(a) CCl_4-Inhalation	7	91.43±25.57	66.74±18.64	6.49±0.30	23.30±4.66
(b) CCl_4-INH c̄ SHP	4	48.75±10.14	42.00± 8.38	6.20±0.43	17.33±0.64
(c) CCl_4-INH c̄ PHL	4	112.75±26.61	54.83±11.77	6.50±0.42	20.88±2.13
(d) CCl_4-INH c̄ STY	5	222.80±58.58	50.00±13.14	6.54±0.43	20.70±1.03
(e) Long-Survival After CCl_4-INH	5	46.00± 4.85	50.10±37.44	6.32±0.41	17.00±1.70
(f) Phenobarbital	5	44.60± 6.19	33.94± 7.64	6.84±0.26	15.54±0.95
(g) Control	9	42.00±13.74	31.12±14.08	6.54±0.43	14.91±1.14
(a') TA-Injected	10	64.20±22.39	74.11±40.77	6.19±0.58	21.23±2.43
(b') TA-Inj c̄ SHP	11	43.91±17.75	68.17±23.03	6.25±0.45	17.96±1.60
(d') TA-Inj c̄ STY	5	84.00±33.11	81.34±20.26	5.80±0.37	20.32±1.82
(e') Long-Survival After TA-Inj	5	54.20± 9.31	38.84±17.33	6.20±0.28	16.34±1.96
(h) Long-Survival After SHP	5	46.40± 4.75	20.02± 8.77	7.12±0.58	14.14±0.86

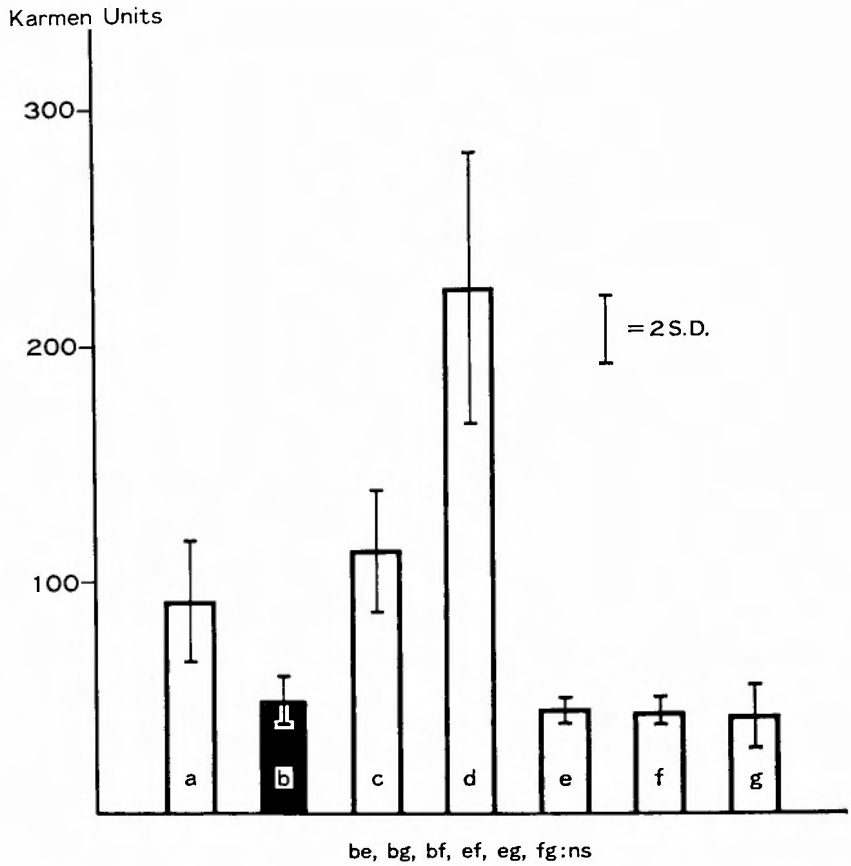

Figure 5. Mean values and standard deviations of SGPT in seven groups : (a) CCl_4-inhalation only, (b) CCl_4-inhalation and SHP, (c) CCl_4-inhalation and PHL, (d) CCl_4-inhalation and STY, (e) long-survival after CCl_4-inhalation, (f) oral administration of phenobarbital and (g) controls. Combinations of two small alphabet letters written under the columns represent the results of statistical treatment; ns means not significant.

and (d'), was not significant, though, (b') was slightly lower than (a') and (d'), as shown in Figure 9. There was no marked difference among all of the experimental groups in relation to serum protein. PAQUET and KAMPHAUSEN[9] injected CCl_4 in rats subcutaneously for eight weeks and followed changes of SGOT, SGPT, alkaline phosphatase and choline esterase, reporting abnormal elevation during the treatment. In administering thioacetamide DONNET, et al[10]. reported rapid elevation in SGPT but no marked change in SGOT or alkalin phosphatase. SGPT in both SHP-groups and alkaline phosphatase in the CCl_4-SHP-group showed a significantly lower mean value than in the groups without SHP. However, alkaline phosphatase in the TA-SHP-group was higher than expected, suggesting that this may depend on the preponderance of intrastitial infiltration of inflammatory cells in the liver of the rats treated with intraperitoneal injection of TA.

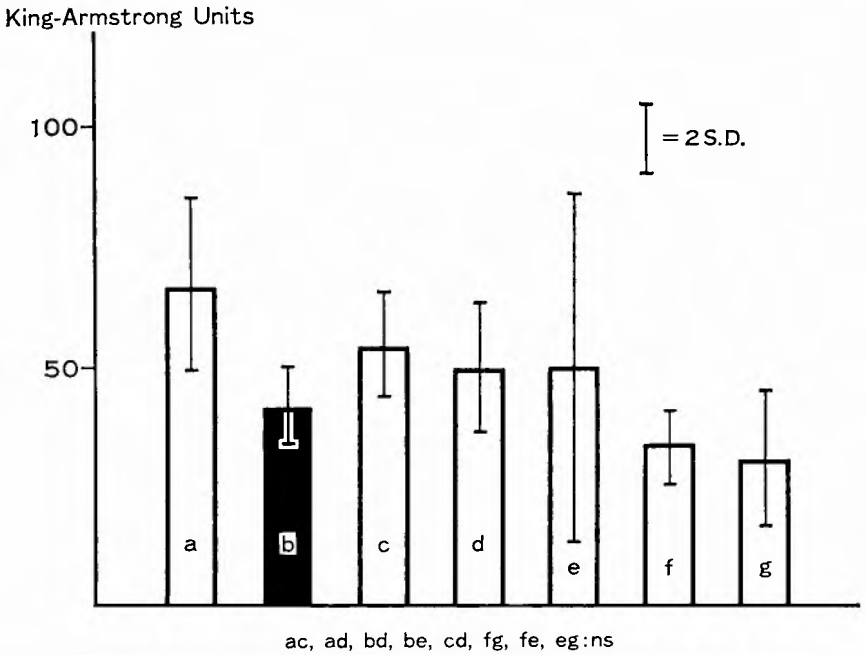

Figure 6. Mean values and standard deviations of alkaline phosphatase in groups (a), (b), (c), (d), (e), (f) and (g).

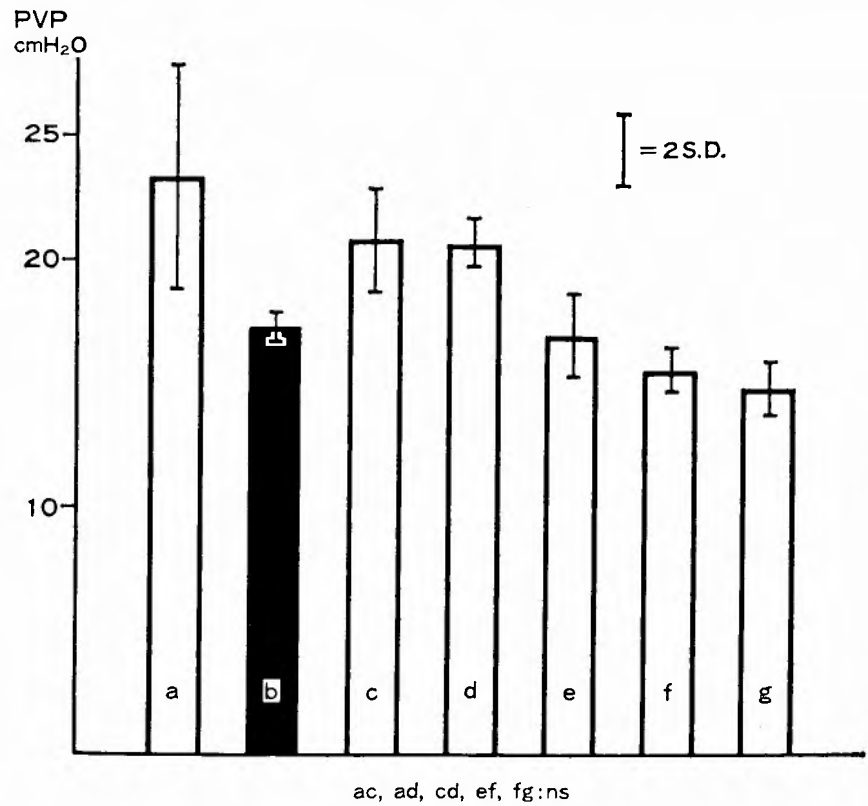

Figure 7. Mean values and standard deviations of portal venous pressure.

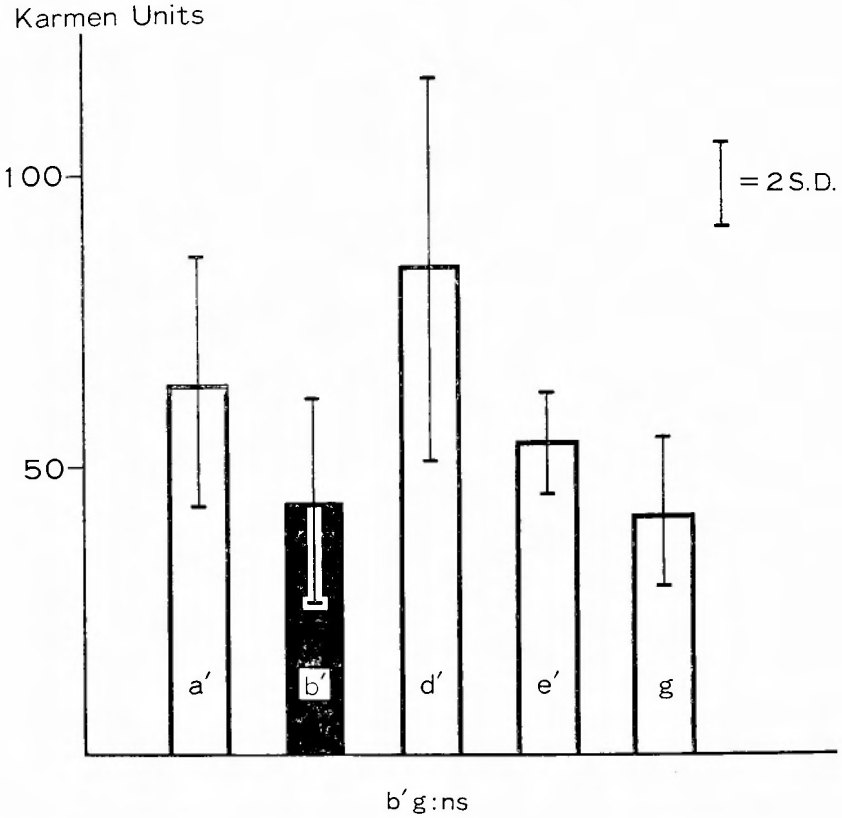

Figure 8. Mean values and standard deviations of SGPT in four TA-treated groups : (a′) cirrhosis induced by intraperitoneal injection of TA, (b′) TA-injection and SHP, (d′) TA-injection and STY and (e′) long-survival after TA-injection, and control group (g).

c) *Portal Venous Pressure (PVP)*: As shown in Table 4 and in Figures 7 and 10, PVP in both SHP-groups was significantly lower than in the other cirrhotic groups. DANIEL, et al[11]. did not find that CCl_4 produced portal hypertension, but BONO, et al.[12] and FUJIMOTO[15] have suceeded in the experimental production of portal hypertension by administering CCl_4 to dogs and rats. In the present study, chemically-induced cirrhosis was always accompanied by portal hypertension.

d) *Histological Findings* : Hematoxylin and eosin stain ; In CCl_4-induced cirrhosis the lobular architecture was distorted by regenerating nodules and divided by a linear hyperplasia of fibrous connective tissue. The liver cells showed marked degeneration with necrosis, atypical nuclei, vacuole formation, etc. There was some difference in the formation of pseudolobules between the TA-and CCl_4-groups; fibrous septa surrounding the regenerating nodules were broader in the former groups. The histological changes in the left lobe in both SHP-groups are shown in Figures 11 and 12. It was difficult to find any difference in cirrhotic alteration between the left lobe and the other lobes. In addition, the cirrhotic

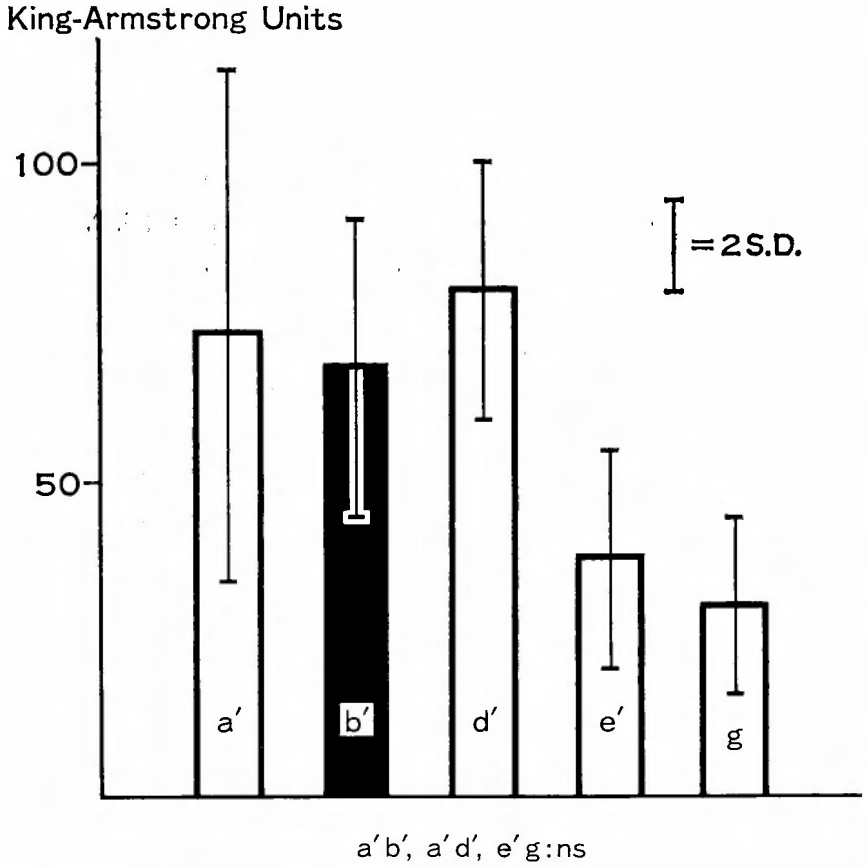

Figure 9. Mean values and standard deviations of alkaline phosphatase in four TA-treated groups : (a′), (b′), (d′) and (e′), and control group (g).

changes in the liver lobes in both SHP-groups were not different from those of groups (a), (c), (d), (a′) and (d″). Van Gieson's stain ; The proliferation of connective tissue was more prominent in the TA-group than in the CCl_4-group. Infiltration of inflammatory cells in the connective tissue was marked in the TA-group, as shown in Figures 13, 14, 15 and 16. There was no improvement in the cirrhosis of the SHP group, as compared with the other cirrhotic groups without SHP. It is said that rats have individual difference in their susceptibility to cirrhogenic agents as well as in their ability to recover spontaneously after the cessation of their administration[4]. In the present study many rats developed typical pseudolobules along with hyperplasia of connective tissue during the administration of CCl_4 or TA, but some rats showed incomplete formation of pseudolobules, or fibrosis. The rats which showed incomplete cirrhotic and/or fibrotic change were omitted from this study.

e) Angiographic Examination : In the majority of rats with SHP, when India ink was injected via the splenic artery it stained the middle portion of the left lobe along a line drawn between the outlet of the hepatic vein and the SHP-site, whereas when the dye was injected via the splenic vein it stained the peripheral area more than in splenic arterial

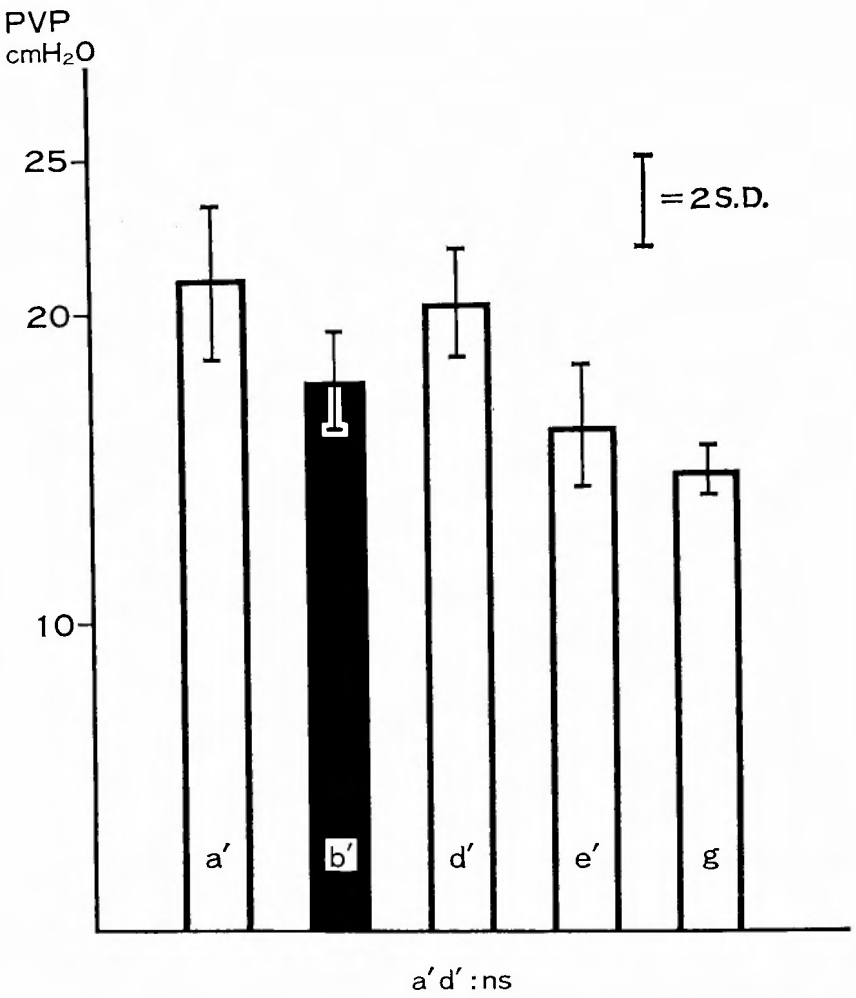

Figure 10. Mean values and standard deviations of portal venous pressure in four TA-treated groups and control group.

angiography, as shown in Figures 3 and 4. India ink was found in the portal venous and hepatic venous branches in fibrous septa surrounding the nodules in splenic venous angiography, as shown in Figure 17.

Discussion

Although there are many types of cirrhosis of the liver, the common pathohistological characteristic is irregular nodular regeneration of the hepatic cells accompanied by hyperplasia of fibrous connective tissue[14]. The regeneration occurs throughout the liver in compensation for the degeneration of liver cells caused by numerous factors such as various hepatotoxic agents, metabolic disturbances, mechanical obstruction of the biliary system, etc.[15], ensuring irreversible alteration of the normal lobular architecture.

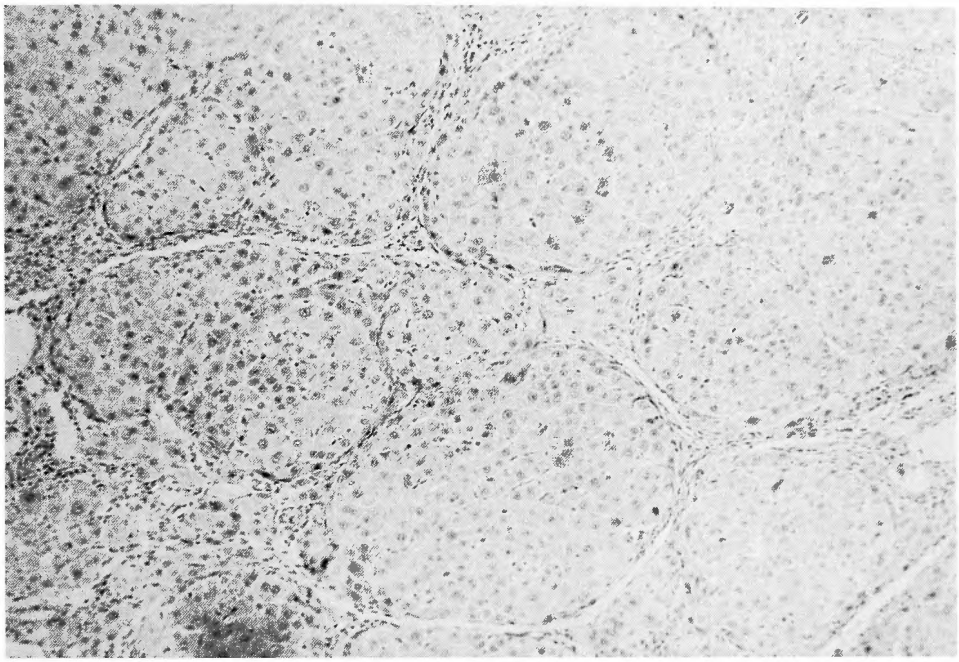

Figure 11. Left lobe of rat receiving CCl_4-SHP. (Hematoxylin and eosin stain)

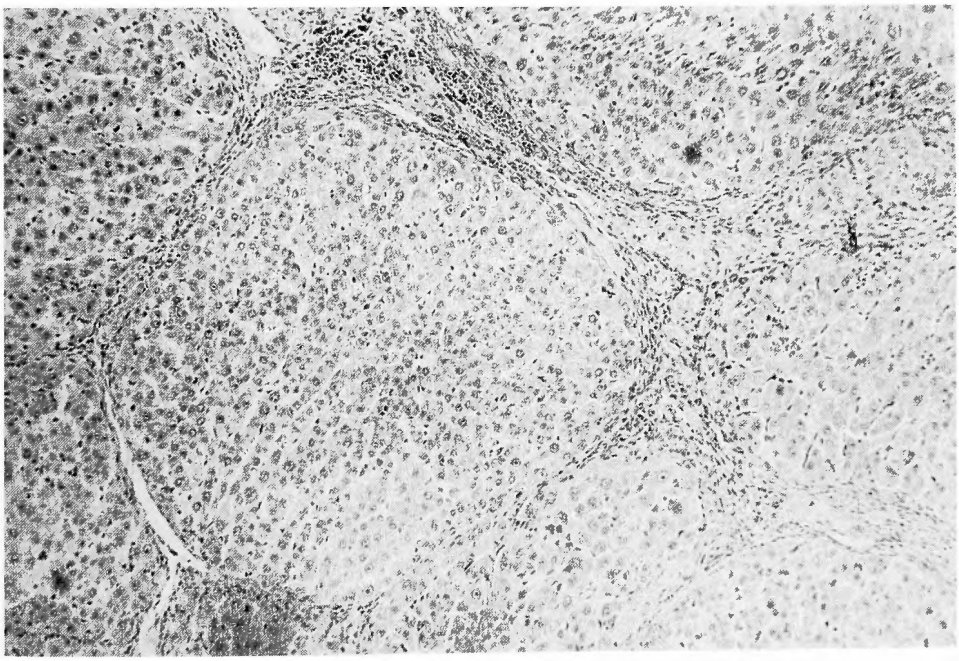

Figure 12. Left lobe : TA-SHP. (Hematoxylin eosin stain)

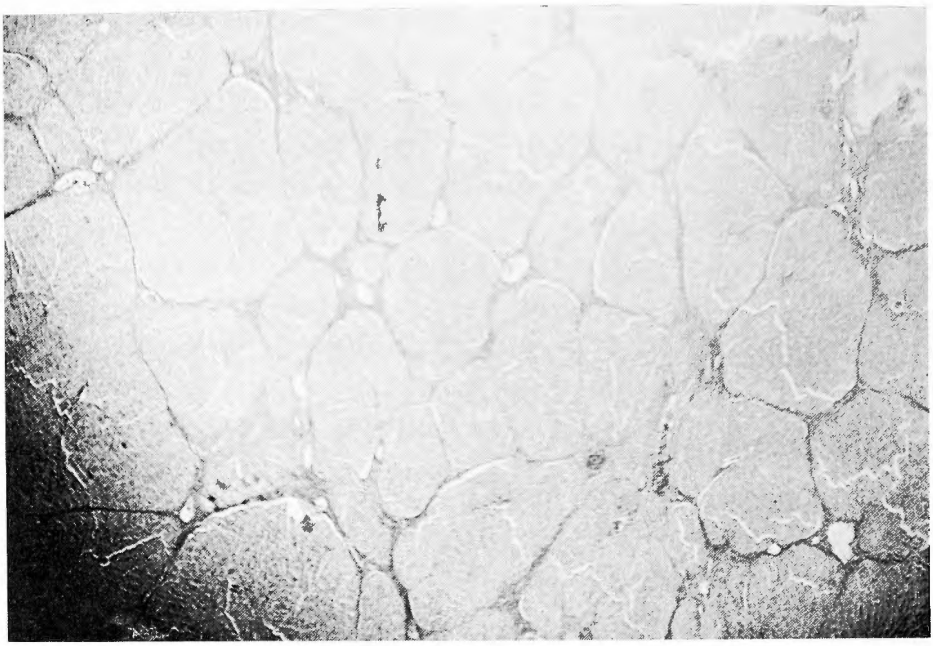

Figure 13. Left lobe : CCl_4-SHP. (Van Gieson's stain)

Figure 14. Left lobe : TA-SHP. (Van Gieson's stain)

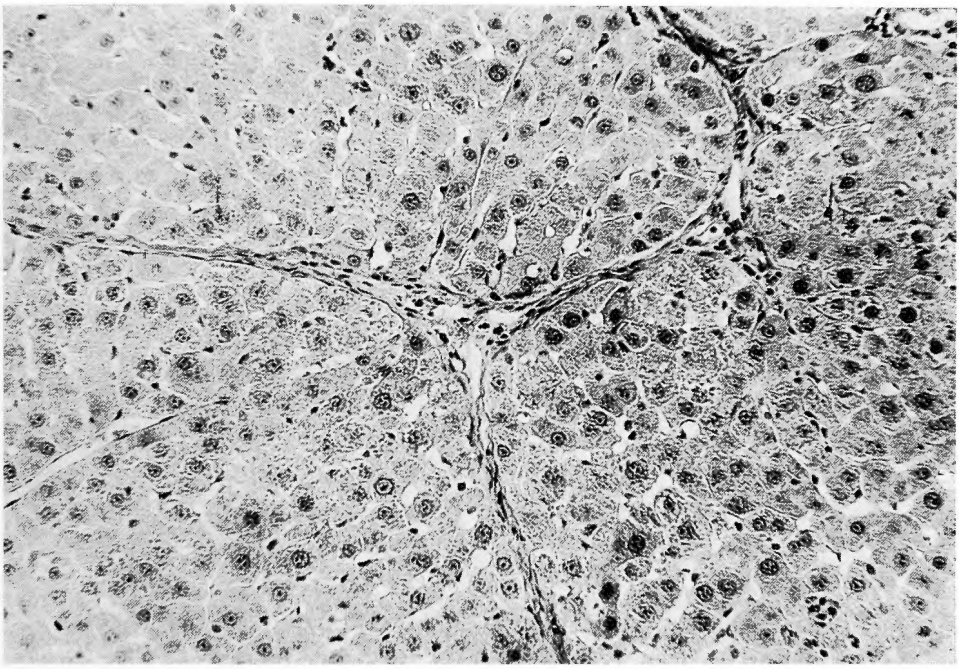

Figure 15. Left lobe of rat receiving CCl_4-SHP. The fibrous septa with slight cellular infiltation are narrower than those of TA-SHP. (VG-stain)

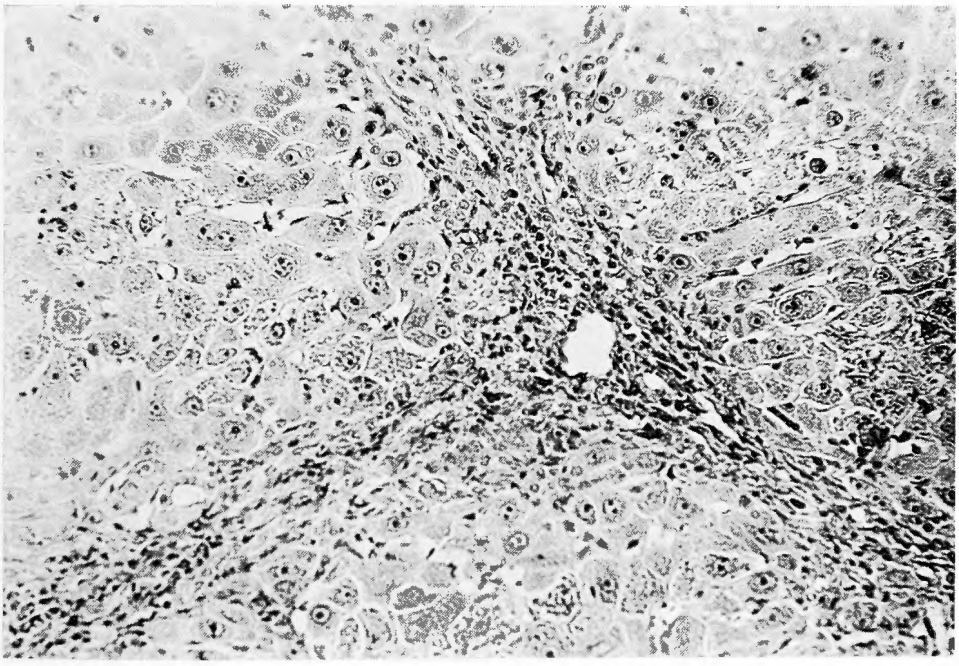

Figure 16. Left lobe : TA-SHP. Marked infiltration of cells in the connective tissue is present. (VG-stain)

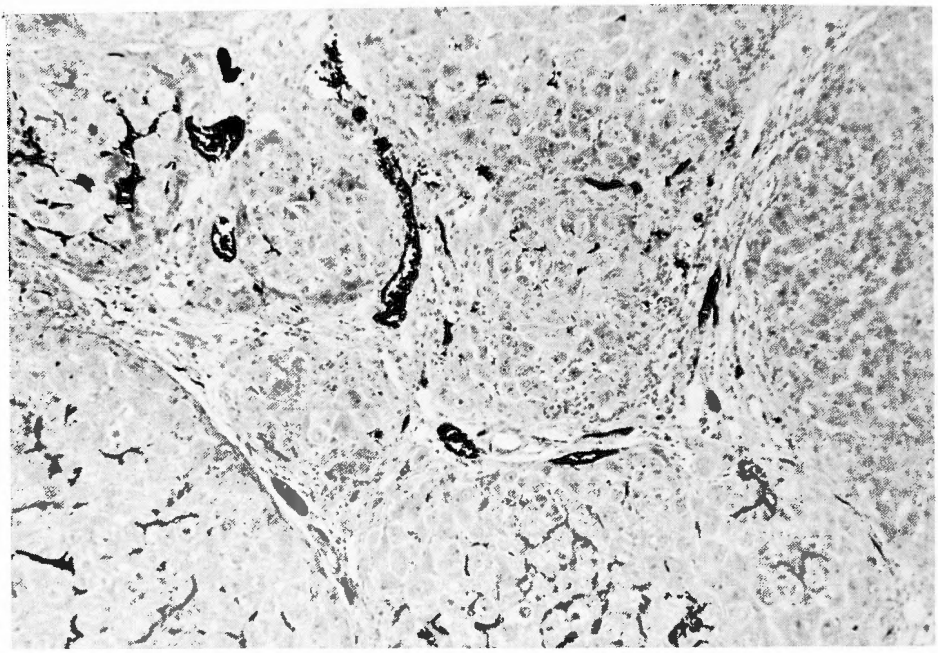

Figure 17. Left lobe : One of the CCl_4-SHP group received injection of India ink via the splenic vein. The dye is found in the vessels in fibrous septa.

Many investigators have succeeded in producing cirrhosis similar to human cirrhosis of the liver in various experimental animals by administring many hepatotoxic chemical agents[16,17] In the present study, two chemical agents, carbon tetrachloride[18] and thioacetamide[19,20] were selected since they were easily obtainable and most reliable in their effects. In the groups of animals which were treated with inhalation of carbon tetrachloride, water containing sodium phenobarbital was given ad libitum throughout the course of the experiment in order to increase their susceptibility to CCl_4-poisoning[2]. Additional administration of CCl_4 or thioacetamide was continued after spleno-hepatoplasty, partial hepatic lobectomy or splenectomy, because HIDA, et al.[21], NAKAJIMA and SHIMOKAWA[22] and FUNAKI[4] reported that rats with chemically-induced cirrhosis often recover quickly after chemical agents were discontinued.

It is said that cirrhosis of the liver may provoke few symptoms and that it has been latent or unsuspected during life in about one third of the cases seen at autopsy[23]. However, an appreciable number of patients with cirrhosis are threatened with sudden death due to massive bleeding from rupture of esophageal varices. In the majority of instances, the disease is accompanied by portal hypertension. Various surgical procedures have been, therfore, devised to control these life-threatening complications. They are currently divided into two categories; one is direct transection of the esophagus for varices[24,25] and the other portosystemic shunt oparations for decompression of portal hypertension[26,27]. In addition, omentopexy[28], hepato-diaphragmopexy[29] or spleno-pneumopexy[30] have been devised to

reduce portal hypertension by facilitating the development of hepatofugal collateral venous channels. However, some of the portosystemic shuntings may decrease the hepatopetal flow of portal venous blood, leading to acute hepatic failure, though they are effective in lowering portal hypertension. Therefore, careful preoperative and operative assessments are always necessary in the selection and application of these procedures[31,32]. Some investigators have succeeded in minimizing untoward side effects such as portal-systemic encephalopathy, hepatorenal syndrome, etc. However, it is no exaggeration to say that the majority of the above-mentioned surgical procedures have been elaborated only for the purpose of treating the complications of cirrhosis of the liver and that none of them is a radical therapeutic approach able to restore the cirrhotic liver to normal.

On the other hand, some investigators have tried to establish more radical therapeutic methods than those mentioned above, e.g. intrahepatic insertion of the greater omentum[33], implantation of the isolated right gastric artery[33] or sewing intestinal loops to the surface of the liver[34] in order to deliver blood to the cirrhotic liver from extrahepatic sources. These measures have been applied experimentally and clinically, but they have not been applied because of uncertainty of their effectiveness. KIMOTO and SUGIE[35] and SUZUKI[36] implanted the splenic artery into the liver parenchyma. They observed that the implanted artery delivered blood to the liver in their animal experiments and applied this technique to human subjects with cirrhosis of the liver as a supplementary method in portosystemic shunt operations. They have, however, reached the conclusion that it had little effect on improving the cirrhotic liver after long-term follow-up studies[33]. DAVIS and MORSE[37] also implanted the splenic artery into the canine liver according to a hint from VINEBERG's operation[38], contemplating improvement in the cirrhotic alteration. GOLDSMITH, et al.[39-42] carried out a series of experiments in dogs. In one of them, they implanted tha splenic artery and vein into the liver separately, observing patency in the artery, but the implanted vein was obstructed easily by thrombus formation unless portal hypetension was maintained. In the other experiment, they used a vascular bundle consisting of artery and vein instead of separate implantations. They resected lobes other than the lobe where the vascular bundle was implanted. They found a compensatory hypertrophy of the remaining lobe, observing neither thrombotic obstruction of the implanted vessels nor hemorrhage into the biliary tract. These implantation techniques seem to have a common weak point, that is obstruction due to thrombus formation. ELIAS and EVANS[43] devised, therefore, a method in dogs in which they implanted a part of the spleen with arterial and venous branches into the liver instead of the freed splenic blood vessels, and noted that patent new pathways formed between the liver and the spleen. This method shows that a direct blood supply to the liver from an extrahepatic source may be possible and may be useful as supplementary treatment in cases of extensive hepatectomy for malignant neoplasms, portocaval shunt oparation, massive hepatic trauma, etc.

BENICHOUX, et al.[44] performed SHP in 13 patients with liver cirrhosis of alcoholic or postnecrotic origin. Two of them died after surgery, one had hemorrhage from recurring

esophageal varices, while the other ten improved. The outline of their SHP-procedure is that they made an incision ten centimeters wide and five centimeters deep in the left lobe, wedged the partially-decapsulated superior portion of the spleen into the wound, closed it by anchoring it with interrupted cat-gut sutures through thin Teflon belts or a Nylon net, and finally fixed both ends to the diaphragm in order to prevent fall-off of the spleen. In their clinical cases, they did not perform any other surgical procedures such as esophageal transection or portosystemic shunt oparations. They confirmed that there was a good blood flow through the SHP-site by spleno-portography in animal models as well as humans. Unfortunately, however, they omitted any comment on the mechanism of SHP. It has not been clarified, therefore, how SHP reduces portal hypertension or what it does to the histological appearence of cirrhosis of the liver. They did not mention any development of collateral venous pathways along the plastic supports, nor did they report any comparison of liver chemistry studies between the cases with SHP and controls.

The present study was designated to determine the effect of SHP on cirrhosis of the liver. SHP was performed in two groups of rats, one of which was treated with carbon tetrachloride and the other with thioacetamide. The former was designated the CCl_4-SHP-group and the latter the TA-SHP-group. In both SHP-groups portal venous pressure decreased significantly. In a few cases, omentum, intestine and/or parietal peritoneum adhered loosely to the SHP-site, but the majority of animals with SHP showed no development of collaterals on gross examination at laparotomy. Alkaline phosphatase and SGPT tended to become normal. A good blood flow through the implanted spleen was demonstrated by arterial and venous angiography with radiopaque and chemical dyes. These observations and data suggest that SHP definitely improved portal hypertension and liver function in rats with cirrhosis. Recently, YASUDA, et al.[45] have reported that rats with SHP survived longer than those without SHP after ligation of the portal venous trunk but not the splenic vein. However, in the present study the majority of rats with SHP did not survive long after complete blockade of the portal venous flow to the liver.

According to GOTO[6] and REIFFERSCHEID, et al.[46], rats with CCl_4-induced cirrhosis survivived hepatectomy of more than 60 per cent and showed regenerative hypertrophy of the remaining liver. However, such a small-scale resection as that of the left lobe only as was done in the SHP-animals seems negligible in respect to the stimulating effect of hepatectomy on regeneration or hypertrophy, because no weight gain of the liver was demonstrated in animals in which the left lobe was resected or in those with SHP. ISLAMI, et al.[47] performed hepatectomy to a maximum of 73 per cent in rats with CCl_4-induced cirrhosis and noted regenerative hypertrophy of the remaining liver, concluding that it was probably induced by the increased supply of portal venous and of arterial blood. However, in the present study, hypertrophy of the lobe into which the spleen was wedged was not found in the majority of rats with SHP. In addition, no difference in macroscopic or microscopic findings in the liver was seen between the groups with left lobe resection and those with resection of the other lobes, nor between the rats receiving SHP and those with partial

hepatic lobectomy or splenectomy.

In all forms of cirrhosis of the liver, portal hypertension is the most common complication, causing debate as to the etiology. There are several factors such as splanchnic blood flow, resistance to hepatic blood flow and pressure on the inferior vena cava. In evaluating the part played by each factor, the increased resistance to hepatic blood flow seems to be the most important[48,49]. In cirrhosis of the liver, the portal vascular bed is distorted by the regenerating nodules and is occluded mechanically during cirrhotic reconstruction of the normal lobular architecture. The central vein is also displaced outward from its original site until it appears in a fibrous septum where it joints the portal venous radicle[48]. When resistance to the intrahepatic blood flow is increased, some of the portal blood is diverted directly into the hepatic venous radicle by bypassing the nodules, while some portal blood is shunted into the extrahepatic collateral veins. SHALDON, et al.[50] reported that one third of the portal blood perfusing the cirrhotic liver was shunted into these venous channels. KESSLER, et al.[51] found in their microangiographic studies that arterioles drained into the venous channel surrounding the nodules instead of into the sinusoids. In short, it is evident that in cirrhosis of the liver more direct pathways are formed between the hepatic arterial and portal venous radicles as well as between the hepatic venous and portal venous radicles than in fibrotic or normal livers[52]. Some investigators claim that arterialization of the portal venous system may exert a harmful influence of portal venous pressure by raising the intrasinusoidal pressure[53,54], while others believe that these intrahepatic arterio-venous shunting may be responsible for portal hypertension in cirrhosis of the liver[55]

In the present study, angiography via the splenic artery revealed that the left lobe was usually stained first at the SHP-site, followed by centripetal spreading of dye in the central area on the under surface of the lobe. When India ink was injected via the splenic vein, staining occurred first near the SHP-site but it spread to the peripheral area more than it did in arterial angiography. The difference in the staining process between the two angiographic examinations suggests that splenic portal blood is diverted to the hepatic venous system through newly formed channels more than is splenic arterial blood. In transplantation of the spleen to the liver, bleeding occurs from the stumps of the arterial and venous branches and from the hepatic arterial and portal branches at the same time. Some of these vascular stumps are closed by thrombus formation, by mechanical compression due to the surgical anastomosing procedure and by vasomotor constriction, while some stumps remain patent to deliver blood to the hepatic venous stumps located in the vicinity. Thus, bridge formation may develop between the hepatic venous branches and the other vascular stumps. The following vascular communications can be formed hypothetically; hepatic arterial to hepatic venous, portal venous to hepatic venous, and splenic arterial to hepatic venous or splenic venous. WAKIM and MANN[56] and HALES, et al.[57] have shown arterio-venous anastomoses between the hepatic artery and the portal vein but not between the hepatic artery and the hepatic vein in normal mammalian livers in situ. BERMAN, et al.[58] have reported that the arterio-venous and veno-venous communications existing in the

normal liver and spleen might become exaggerated in cirrhosis of the liver. The artery delivers a small volume of blood under high pressure, while the portal vein supplies large volume of blood under low pressure. From the standpoints of anatomy and hemodynamics, the distribution of the arterial stumps in the hepatic and splenic sections is much less than in the portal venous stumps. The sum of the cross-sectional area of the arterial stumps is assumed to be much smaller than that of the portal stumps and hence the blood volume expelled per unit of time from the former should be much less than that of the latter. This assumption may be correct because when India ink was injected via the splenic vein it stained the lobe diffusely more than it did in splenic arterial angiography with the same pressure of injection. This suggests the possibility that SHP directly or indirectly diverted portal blood to the hepatic venous system through newly formed veno-venous communications more than did the pre-existing bypasses in cirrhosis, leading to decompression of portal hypertension. Contrary to expectation, however, SHP delivered blood into the sinusoids but not enough to induce regeneration of the liver cells. The improvement of some of the liver chemistry studies in rats with SHP may be due partly to the decrease in portal venous pressure or the small increase of splenic arterial or venous blood to the sinusoids. Recently, OKAJIMA, et al.[59] have reported that SHP caused numerous vascular communications to develop between the liver and the spleen, through which splenic arterial and venous blood was delivered to the sinusoids and the hepatic portal vein, contributing to the development of intrahepatic short circuits between the hepatic vein and the portal vein as well as to augmentation of the effective hepatic blood flow. They found improvement in the wedge pressure of the hepatic vein and in the A/G ratio but not in the other liver chemistry studies.

The results of the present study indicate that SHP may be a valuable procedure in the treatment of cirrhosis of the liver. In general, many investigators and surgeons are very suspicious about SHP, because it is a paradoxical procedure different from conventional surgical therapeutic methods. It is worthwhile to mention that SHP played an important role in reducing portal hypertension by diverting the portal venous blood to the hepatic vein on the one hand, while nourishing the liver cells, though insufficiently, on the other hand. SHP is not so difficult as to require highly specialized techniques, although it may be accompanied by occasional massive bleeding or difficulty in transplantation of the spleen. This suggests that SHP may be applicable in even severe cases in which the effective volume of blood perfusing the cirrhotic liver is estimated to be less than one third of the normal value, since the additional blood supply from the spleen may be enough to prevent acute hepatic failure which often occurs after portosystemic shunt oparations. The following questions have arisen from the present study : What is the role of the artery in the development of arterio-venous and veno-venous shunting pathways between the liver and spleen? What vascular communications exist other than those confirmed in this study? How much splenic arterial or venous blood distributed to the hepatic sinusoids, the hepatic portal vein, the hepatic vein, etc ? The most important problem is the difference between human

subjects with cirrhosis of the liver and animal models. This procedure should, therefore, be given a clinical trial on the basis of the knowledge obtained from the present experiment.

Conclusion

1) Cirrhosis of the liver was produced in rats by CCl_4 or TA.

2) Portal hypertension with abnormal liver chemistry studies were found in the majority of rats with cirrhosis.

3) Rats treated with spleno-hepatoplasty (SHP) showed a significant decrease in portal venous pressure and improvement in alkaline phosphatase and SGPT.

4) Arterial and venous angiography demonstrated good blood flow to the liver through the site of SHP in rats with cirrhotic livers and in those with normal livers.

5) In splenic venous angiography India ink stained diffusely the left lobe, the site of SHP, more than it did in splenic arterial angiography.

6) This finding suggests that in the various vascular communications between the liver and the spleen splenic venous to hepatic venous shunting is the most important for the decompression of portal hypertension.

7) SHP did not result in any histological improvement in rat liver cirrhosis.

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和文抄録

肝硬変症に対する Spleno-Hepatoplasty に関する実験的研究

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肝硬変症においては，その特徴的な肝の病理組織学的所見とともに，臨床的には肝機能の異常や門脈圧亢進症にともなう種々の症状がみられる．今日までこれらを制御するために多くの研究がなされ，外科的な方策としては食道静脈瘤に対する直達手術と，門脈下大静脈系のシャント手術が確立している．

しかしこれらの外科的方法はあくまで対症的なものであるといってよく，真に肝硬変症における肝細胞の変性や崩壊を抑止し，間質結合織の増加をも抑制または減少させるものではない．

1964年に Benichoux & Barlier は Spleno-Hepatoplasty (SHP，脾肝接合術) について報告し，1971年には臨床例においても良好な結果を得たとしているが，その機作については詳述していない．

著者はラットに四塩化炭素またはチオアセトアミドの2種の硬変形成物質を投与して，2群の肝硬変を作製し，これに SHP を施行し，肝重量，組織学的変化，門脈圧および肝機能検査値について検討した．

SHP 施行後に肝重量は増加せず，SHP 施行葉においても重量増加や硬変像の軽快はみられなかったが，門脈圧は SHP 非施行の硬変群に比べて有意に低下し，肝機能検査値も改善を示した．

India ink を用いての脾静脈経由の造影では SHP 施行肝葉は広範にそまり，脾動脈経由のそれは同葉接合術部を中心として肝静脈への流出部へとより狭少な着色を示した．これは脾および肝の接合面において，解剖学的および血行動態上，脾静脈門脈間の吻合の生じ易いことを示唆すると思われる．

当初肝に対する脾よりの血流供給増加により，変性崩壊の過程にある肝小葉に十分な血液供給を生じて，肝硬変の進行停止ないし軽快を得るのではないかと考えたが，当実験ではむしろ肝内シャントの作製が主と思われた．しかし，SHP 施行ラットの門脈結紮では，非施行ラットに比べ長時間生存が得られ，肝機能検査値の改善も門脈圧正常化による効果に加えて，類洞への血流増加による故もあると推察され，今後さらに検討していきたい．

臨床例に応用の際は，従来の術前検査により適応外とされていた重度の肝硬変に対しても，侵襲の軽いことや手技に繁雑さのないことから可能と考えられ，上記の血行動態についての研究と合わせて適用していきたい．